

# L-Proline promoted Ullmann-type reaction of vinyl bromides with imidazoles in ionic liquids†

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Received (in Cambridge, UK) 3rd February 2005, Accepted 6th April 2005

First published as an Advance Article on the web 21st April 2005

DOI: 10.1039/b501628b

The Ullmann-type coupling reaction of vinyl bromides and imidazoles in ILs at 90–110 °C gave the corresponding *N*-vinylimidazoles in good to excellent yields by using L-proline as the ligand; the double bond geometry of the vinyl bromides was retained under the reaction conditions.

*N*-Vinylimidazoles are valuable intermediates in organic synthesis. They have been widely employed as building blocks in the synthesis of metal complexes, and also as intermediates in the synthesis of various heterocycles and poly(*N*-vinylimidazole)s which have found growing applications in metals separation, polar compounds extraction, cosmetics and coloring matter refinement.<sup>1</sup> In addition, *N*-vinylimidazoles have found antifungal and antiparasitic applications in medicine and agriculture.<sup>2</sup>

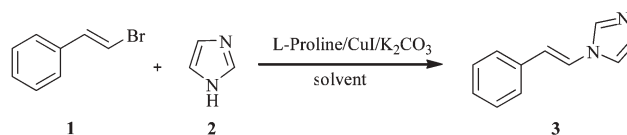
Conventionally, protocols for their preparation include direct addition of imidazoles to alkynes,<sup>3</sup> *N*-vinylation of imidazole with vinyl halides or acetates,<sup>4</sup> copper-catalyzed C–N bond cross-coupling with vinylboronic acid,<sup>5</sup> and olefination of  $\beta$ -hydroxyimidazoles.<sup>6</sup> Although these protocols provide access to *N*-vinylimidazoles, they suffer from either harsh reaction conditions or lack of stereocontrol of the double bond geometry.

On the other hand, in recent years, great interest has been shown in the metal-catalyzed C–N bond formation of aryl halides.<sup>7</sup> Most of the work has concentrated on the formation of aromatic C–N bonds, with only one example of the palladium-catalyzed vinylation of azoles reported.<sup>8</sup> In contrast, vinylic C–N cross-coupling reactions have been demonstrated using copper as the catalyst or promoter.<sup>9</sup> Surprisingly, although the copper-catalyzed coupling of aryl halides with imidazoles has been extensively applied to synthesize the *N*-arylimidazoles,<sup>10</sup> the application of the same cross-coupling reaction to vinyl halides has not been described. Herein, we wish to report the synthesis of *N*-vinylimidazoles by using CuI as the catalyst and L-proline as the ligand.

Ionic liquids (ILs) as the novel “solutions” for transition metal catalysis have been widely studied in recent years.<sup>11</sup> Various metal-catalyzed reactions, including copper-catalyzed Ullmann-type reaction,<sup>12</sup> have been demonstrated in ILs and excellent results have been obtained. Our experiment was first conducted by coupling  $\beta$ -bromostyrene and imidazole catalyzed by 10 mol% CuI and 20 mol% L-proline (Scheme 1). This reaction proceeded well at 90 °C in IL [Bmim]BF<sub>4</sub> in the presence of K<sub>2</sub>CO<sub>3</sub> to produce *N*-styrylimidazole in 80% yield (Table 1, entry 1). Higher yield and shorter time were obtained by raising the reaction temperature

(entry 2). Without the addition of L-proline the reaction gave only 9% yield for the same reaction time and temperature (entry 3). Among the solvents tested, [Bmim]BF<sub>4</sub> gave the best result, ILs with other different anions and MeCN provided slightly lower yields, while DMSO and DMF delivered little desired coupling product (compare entries 4–9). Furthermore, when the same anion IL based on the pyridine was used as the reaction medium, a similar result was obtained for the same reaction time and temperature (entry 10). It seems that different anions of the ILs have different effects on the reaction rate or yield, and the cation has little effect on them in our novel reaction system.

After optimized reaction conditions were obtained, the reaction scope was explored with various vinyl bromides and other imidazoles. The results are summarised in Table 2. It was found that either electron-rich or electron-deficient vinyl bromides were suitable for this reaction, giving the desired coupling products in good to excellent yields. We found, however, that *Z*-vinyl bromides were not suitable substrates, most likely because of their increased level of steric hindrance. In contrast, this protocol was less sensitive to the size of imidazoles used. For example, benzimidazole performed well under the reaction conditions and



**Scheme 1** CuI-catalyzed coupling reaction of  $\beta$ -bromostyrene **1** with imidazole **2**.

**Table 1** Formation of **3** under different catalytic conditions

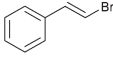

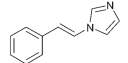

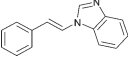

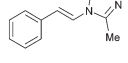
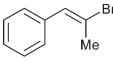

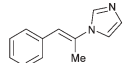
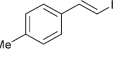

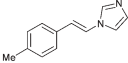

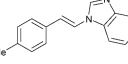
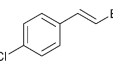

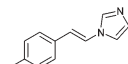

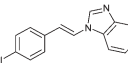
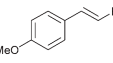

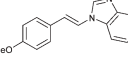
Entry	Solvent	<i>T</i> /°C	<i>t</i> /h	Yield (%) <sup>a</sup>
1	[Bmim]BF <sub>4</sub>	90	30	80
2	[Bmim]BF <sub>4</sub>	110	20	87
3	[Bmim]BF <sub>4</sub>	110	20	9 <sup>b</sup>
4	[Bmim]PF <sub>6</sub>	110	20	70
5	[Bmim]Br	110	30	78
6	[Bmim]I	110	30	60
7	MeCN	reflux	36	25
8	DMSO	110	30	— <sup>c</sup>
9	DMF	110	30	— <sup>c</sup>
10	[Bpy]BF <sub>4</sub>	110	20	85

<sup>a</sup> Isolated yield. <sup>b</sup> L-proline was not used. <sup>c</sup> Little coupling product was determined. <sup>d</sup> Bmim = 1-butyl-3-methylimidazolium. Bpy = *N*-butylpyridinium. <sup>e</sup> Reaction conditions:  $\beta$ -bromostyrene (2 mmol), imidazole (2.2 mmol), CuI (0.2 mmol), L-proline (0.4 mmol), K<sub>2</sub>CO<sub>3</sub> (5 mmol) in 4 mL suitable solvent.

† Electronic supplementary information (ESI) available: experimental section. See <http://www.rsc.org/suppdata/cc/b5/b501628b/>

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**Table 2** *N*-Vinylimidazoles synthesized with CuI/L-proline/IL system

Entry	Vinyl bromide	Imidazole	Product	<i>t</i> /h	Yield (%) <sup>a</sup>
1				20	87
2				20	88
3				30	60
4				20	75
5				20	86
6				20	86
7				20	93
8				20	91
9				20	85

<sup>a</sup> Isolated yield. <sup>b</sup> Reaction conditions: vinyl bromide (2 mmol), imidazole (2.2 mmol), CuI (0.2 mmol), L-proline (0.4 mmol), K<sub>2</sub>CO<sub>3</sub> (5 mmol) in 4 mL [Bmim]BF<sub>4</sub> at 110 °C.

afforded the desired *N*-vinylimidazoles in excellent yield (entries 2, 6, 8, 9). For the sterically hindered substrate, 2-methylimidazole, a longer reaction time was required to consume the starting material, and a slightly lower yield was observed (entry 3).

Another merit of ILs in the metal-catalyzed reaction is that the metal catalysts immobilized in these media can be reused.<sup>11,12</sup> To evaluate the possibility of recycling the CuI/L-proline/IL used for

**Table 3** Reuse of CuI/L-proline/IL reaction system

Cycle	Yield (%) <sup>a</sup>	Cycle	Yield (%) <sup>a</sup>
1	87	3	82
2	85	4	83

<sup>a</sup> Isolated yield. <sup>b</sup> Reaction conditions: β-bromostyrene (2 mmol), imidazole (2.2 mmol), CuI (0.2 mmol), L-proline (0.4 mmol), K<sub>2</sub>CO<sub>3</sub> (5 mmol) in 4 mL [Bmim]BF<sub>4</sub> at 110 °C for 20 h.

the reaction, β-bromostyrene, imidazole, CuI, L-proline and K<sub>2</sub>CO<sub>3</sub> in [Bmim]BF<sub>4</sub> were allowed to react in the ionic solvent for 20 h and then the products were extracted with ethyl acetate (3 × 2 mL). After the recovered ionic solvent was concentrated *in vacuo* (5.0 torr for 1.5 h at 60 °C), further amounts of reactants and K<sub>2</sub>CO<sub>3</sub> (2 mmol) were added and the process was repeated up to four times, until the build-up of KBr rendered the mixture solid-like at room temperature.<sup>13</sup> It seems that there is little effect on the rate or yield of the reaction during each cycle (Table 3).

In summary, we have developed a mild and efficient method for the copper-catalyzed coupling of imidazoles with vinyl bromides. The use of ionic liquids as excellent media for the coupling reaction has been demonstrated. The mild reaction conditions and high stereoselectivity relative to previous methods, the operational simplicity, and recyclable metal-catalyzed reaction system should render this protocol attractive to synthetic chemists.

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- 13 Investigations on recycling of [Bmim]BF<sub>4</sub> are in progress.